REMARKS

Applicant received a first restriction requirement on July 30, 2003. In their Response, Applicant pointed out that the Examiner had apparently issued that restriction based upon the claims of the *parent* case (which matured into U.S. Patent No. 6,284,879). The present application, however, is a *continuation-in-part* of the parent case and contains different and additional claims from its parent application. In this Office Action, the Examiner has acknowledged the error, withdrawn the previous restriction requirement, and issues a new restriction requirement.

In the new restriction requirement, Claims 1-42 have been restricted among 8 groups:

Group I (Claims 1-3, 5-8, 11-15, 17-21, 23-27, and 29-30) drawn to nucleic acids encoding a TAP2 splice variant, vectors encoding said nucleic acids, host cells transformed with said vectors, methods of producing polypeptides using said host cells, and methods of altering peptide transport in a cell using nucleic acids;

Group II (Claims 1-2, 4, 7-8, 10, 13-14, 16, 19-20, 22, 25-26 and 28) drawn to nucleic acids encoding a TAP1 splice variant, vectors encoding said nucleic acids, host cells transformed with said vectors, methods of producing polypeptides using said host cells, and methods of altering peptide transport in a cell using said nucleic acids;

Group III (Claims 31, 35, and 36) drawn to TAP1 splice variant polypeptides;

Group IV (Claims32-34) drawn to TAP2 splice variant polypeptides;

Group V (Claims 37-39) drawn to antibodies;

Group VI (Claims 40) drawn to methods for treating a disorder comprising gene therapy to provide normal TAP heterodimer expression;

Group VII (Claim 41) drawn to methods for broadening the immune response by introducing lymphocytes transfected *ex vivo* to express a TAP isoform; and

Group VIII (Claim 42) drawn to a method for diagnosing or monitoring a disease comprising determining the expression of a TAP isoform in a sample.

Applicant acknowledges that the Examiner considers Claims 1-2, 7-8, 13-14, 19-20, and 25-26 to be linking claims, i.e., upon allowance of any of the linking claims, the restriction requirement as to the linked inventions shall be withdrawn and any claims(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application.

In restricting the claims, the Examiner reasons as follows:

> "1) Inventions I and II, and inventions III and IV are separately patentable inventions each from the other. TAP1 and TAP2 are separate and distinct genes which comprise distinct nucleic acid sequences encoding distinct polypeptides. The TAP1 and TAP2 gene products are not equivalent in function or structure and have distinct physical, chemical, and functional properties. As such, it is proper to separate two distinct genes encoding distinct proteins each from the other.
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> 2) Inventions I and III, and Inventions II and IV are related to each other in part as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP §806.05(f)). In the instant case, the polypeptides of inventions III and IV can be made by using an amino acid synthesizer, or by isolating said naturally occurring polypeptides from human cells, and do not require the nucleic acids of inventions of inventions I and II. Furthermore, nucleic acids and polypeptides are not related in that nucleic acids have substantially different physical, structural, chemical, and functional properties than polypeptides, are made using different reagents and methods, and are used for substantially different purposes, such as the use of the nucleic acids in hybridization assays.
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> 3) Inventions I-IV are further patentably distinct from invention V in that the nucleic acids, vectors and host cells of inventions I-II, the

polypeptides of invention III and IV, and the antibodies of invention V have substantially different structures and properties, are made using substantially different techniques, have different modes of operation, different functions, and different effects, and can be used for substantially different purposes.

4) Inventions I and II are patentably distinct from invention VI in that the methods of invention VI is an *in vivo* method of treating a disease using gene therapy, whereas the methods of invention I are directed to *in vitro* methods comprising cells in culture. Further, the methods of invention VI can be practiced without the nucleic acids of inventions I and II. The method of gene therapy in invention VI is very broad. It reads on diseases associated with overexpression of the TAP isoforms is not clear. Thus, nucleic acids other than those recited in inventions I and II may be required to achieve normal TAP heterodimer expression.

5) Inventions I and II are patentably distinct from invention VII. The cells of inventions I and II may be used for substantially different purposed than introduction into a mammal for broadening an immune response, such as the use of the cells to produce protein in cell culture, or the use of the cells in vitro assays. Further, the methods of inventions I and II are cell culture methods that do not include the additional steps in invention VII directed to re-introducing the cells into an individual, and also determining TAP isoform expression in the individual.

7) [sic] Inventions III-V are patentably distinct from inventions VI and VII in that the methods of invention VI and VII involve the use of nucleic acids and do not require or depend on the polypeptides and antibodies of invention III-V.

8) [sic] Inventions I-VII are patentably distinct from invention VIII in that the diagnostic method of invention 8 does not require the nucleic acids, proteins, or antibodies of inventions I-V for its practice, since the method involves the detection of protein or mRNA. Further, while the method of invention VII includes a detection step, the method of invention VII further requires transfecting cells with a TAP isomer and administering the cells to an individual not required for invention VIII. (Office Action, pages 4-6.)

Applicant traverses. Applicant points out that this application is a United States national filing under 35 U.S.C. §371; accordingly, this application is subject to the broader "unity of invention" standard (not restriction) as set forth in 37 CFR 1.475. MPEP § 1893.03(d) states:

"The principles of unity of invention are used to determine the types of claimed subject matter and the combinations of claims to different

> categories of invention that are permitted to be included in a single international or national stage patent application. The basic principle is that an application should relate to only one invention or, if there is more than one invention, that applicant would have a right to include in a single application only those inventions which are so linked as to form a single general inventive concept.
> **A group of inventions is considered linked to form a single general inventive concept where there is a technical relationship among the inventions that involves at least one common or corresponding *special technical feature.*** The expression special technical features is defined as meaning those technical features that define the contribution which each claimed invention, considered as a whole, makes over the prior art." (MPEP §1893.03(d), emphasis added.)

As previously discussed, the present invention relates to the discovery of previously unknown isoforms homologous to the known TAP protein subunits. The newly discovered isoforms are the result of alternate RNA splicing and are co-expressed with the known TAP1 and TAP2 gene products, providing a plurality of TAP heterodimers functioning to translocate antigen peptides from the cytoplasm into the endoplasmic reticulum for complexing with MHC class I molecules and formation of MHC class I antigen complexes. The splice variant isoforms have been found to form TAP heterodimers that transport a different repertoire of peptides or that transport similar peptides at different rates than the known TAP1/TAP2 heterodimer. The discovery of these alternative TAP transporter proteins exposes a genetic mechanism of diversification in the process of MHC class I antigen presentation. Co-expression of multiple TAP1 and TAP2 splice variants provides a diverse family of transporters capable of translocating a wider range of antigen peptides from the cytosol to the ER and increasing the repertoire of MHC class I antigen complexes presented to the immune system. It is through such diversification mechanisms that it is now demonstrated that the antigen processing and presentation mechanisms of the immune system are able to drive and select T cell response diversity of the recognition side of the immune system, which is based on the enormous diversity of the T cell receptor.

It is clear from the application as filed that whether the claims recite TAP1 or TAP2 isoform nucleic acids, host cell/expression vectors containing the nucleic acid, TAP1 or TAP2 isoform polypeptides, and the related methods of use, they share a unifying special technical feature which confers novelty over the art, i.e., the discovery of the existence of splice variants of transporter associated with antigen processing, or TAP, proteins and the increased adaptability of the immune system embodied by that discovery.

Accordingly, Applicants request reconsideration of the restriction in view of the unifying special technical feature discussed above.

Conclusion and Provisional Election

Applicant submits that in view of the foregoing remarks all the claims as originally filed are seen to relate to a single inventive concept and share a unifying special technical feature, and the claims are in a form and are of the sort that is properly viewed as relating to a single invention that should not be restricted. Applicant therefore requests that the restriction requirement of the Office Action of December 19, 2003 be reconsidered and withdrawn.

Although, for reasons set forth above, Applicant believes that the restriction is improper and uncalled for, and without in any way acquiescing in the reasons for the requirements set forth in the Office Action, but in order to be fully responsive to the Office Action, Applicant provisionally elects for examination the claims of Group I, i.e., Claims 1-3, 5-8, 11-15, 17-21, 23-27, and 29-30.

Respectfully submitted,

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